Digestion, **15**, 188 (1977).
(16) L. A. Turnberg, *ibid.*, **9**, 357 (1973).
(17) W. H. Halliwell, D. A. Schmidt, and D. P. Hutcheston, *Am. J. Physiol.*, **196**, 74 (1976).
(18) E. Y. Berger, G. Kanzaki, M. A. Homer, and J. M. Steele, *ibid.*, **196**, 74 (1956).
(19) W. H. Barr and S. Riegelman, *J. Pharm. Sci.*, **59**, 154 (1970).
(20) R. K. Nayak and L. Z. Benet, *J. Pharmacokinet. Biopharm.*, **2**, 417 (1974).
(21) P. R. Reeves, D. G. Barnfield, S. Longshaw, D. A. D. McIntosh, and M. J. Winrow, *Xenobiotica*, **8**, 305 (1978).
(22) *Ibid.*, **8**, 313 (1978).
(23) J. W. Paterson, M. E. Connolly, C. T. Dollery, A. Hayes, and R. G. Cooper, *Eur. J. Clin. Pharmacol.*, **2**, 127 (1970).
(24) D. G. Shand, G. H. Evans, and A. S. Nies, *Life Sci.*, **10**, 1417 (1971).
(25) J. T. Doluisio, W. G. Crouthamel, G. H. Tan, J. V. Swintosky, and L. W. Dittert, *J. Pharm. Sci.*, **59**, 72 (1970).
(26) M. L. Lucas, J. A. Blair, B. T. Cooper, and W. T. Cooke, *Biochem. Soc. Trans.*, **1976**, 154.
(27) J. McAinsh, *Postgrad. Med. J., Suppl. 3*, **53**, 74 (1977).
(28) J. D. Fitzgerald, R. Ruffin, K. G. Smedstad, R. Roberts, and J. McAinsh, *Eur. J. Clin. Pharmacol.*, **13**, 81 (1978).

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Bioavailability of Orally Administered Propiram Fumarate in Humans

C. A. KORDUBA ˣ, J. VEALS, E. RADWANSKI, S. SYMCHOWICZ, and M. CHUNG

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Abstract □ Propiram bioavailability was determined in 10 healthy volunteers after a single oral administration of 50 mg (base equivalent) of propiram fumarate in tablet or solution dosage form in a randomized crossover design. The plasma drug concentration–time curve revealed a one-compartment open model with first-order absorption kinetics. There were no statistically significant differences ($p > 0.05$) between all of the measured pharmacokinetic parameters obtained from the tablet and the solution with the exception of the absorption lag time (t_{lag}), where the tablet had a significantly longer t_{lag}. The drug given as a tablet or solution was absorbed rapidly after oral administration with an apparent absorption rate constant of 3.7 hr^{-1} for both dosage forms. The C_{max} value (308 ng/ml for the tablet and 342 ng/ml for the solution) was attained at ~1 hr after oral administration. The elimination half-life was 5.2 hr for the tablet and 4.4 hr for the solution, and the apparent distribution volume was 2.31 liters/kg for the tablet and 1.94 liters/kg for the solution. Total body clearance was much greater than renal clearance, indicating extensive metabolic clearance for both dosage forms. The study showed that propiram administered as the tablet was bioequivalent to the solution.

Keyphrases □ Propiram—bioavailability in humans, tablet *versus* solution □ Hydrolysis—fluorescence analysis, despropionylpropiram □ Bioavailability—orally administered propiram in humans □ Antispasmotics—propiram, tablet *versus* solution bioavailability in humans

Propiram fumarate, *N*-(1-methyl-2-piperidinoethyl)-*N*-2-pyridylpropionamide fumarate, was shown in clinical studies to have analgesic efficacy following oral and parenteral administration. The drug was active in dogs, cats, mice, rats, rabbits, and humans (1, 2) and displayed no physical dependency, carcinogenicity, embryo toxicity, or influence on general reproductive performance (3).

Although pharmacokinetic studies of propiram fumarate in animals (3) and humans (3, 4) have been reported, a detailed pharmacokinetic analysis of the plasma propiram concentration–time data is not available. Thus, the present study was conducted to provide comprehensive information on propiram pharmacokinetics and bioavailability in healthy volunteers after a single oral administration of propiram fumarate in a tablet or solution.

EXPERIMENTAL

Drug Formulation—Two preparations containing propiram fumarate were tested, propiram fumarate tablet[1] and propiram fumarate solution[2] containing 50 mg as propiram.

Study Protocol—Ten healthy male adult volunteers (25–40 years of age) participated. Routine laboratory profiles including a complete blood count, urinalysis, and chemistry panel were obtained prior to the study and 48 hr after drug administration.

The study, a randomized crossover design, was composed of two segments. In the first segment, after an overnight fast, each subject received a single dose of propiram fumarate (equivalent to 50 mg of base) as a tablet or solution with 100 ml of water according to a random code. After at least a 4-day washout period, the subjects were given the other dosage form. No food was allowed until the 4th-hr blood sample was collected, after which a low-fat meal was given.

Blood samples were obtained at 0, 0.5, 0.75, 1.0, 1.5, 2.0, 2.5, 3, 4, 5, 8, 12, 16, and 24 hr. The plasma was separated by centrifugation and stored frozen until it was assayed.

Urine was collected prior to drug administration and for two intervals, 0–24 and 24–48 hr, after drug administration. The total volume of each collection was measured, and an aliquot was frozen until it was assayed.

Assay—A modified method of Pütter and Kroneberg (3) was used. The propionyl group was removed from propiram by acid hydrolysis, and the formed secondary amine (despropionylpropiram) showed a strong fluorescence at specific wavelengths in acidic solution.

Five milliliters of plasma, or 0.5 ml of urine sample plus 4.5 ml of water, was adjusted to pH 11 with 5 *N* NaOH and extracted with 7 ml of toluene. Six milliliters of the toluene phase then was extracted with 3 ml of 1 *N* H_2SO_4. An aliquot of the acidic aqueous phase (2.5 ml) then was transferred to a 3-ml serum bottle[3]. After the air was displaced with argon, the vial was closed with a stopper[4] and aluminum seal and placed in a manifold block[5] heater for 4 hr at 120°. After cooling to room temperature, the fluorescence of the formed despropionylpropiram was measured at 314 (excitation) and 380 (emission) nm in a spectrophotofluorometer[6].

[1] FMR 76228D-06, batch 8747-40, Schering Corp., Bloomfield, N.J.
[2] FMR 77571D, batch 9383-44, Schering Corp., Bloomfield, N.J.
[3] No. CA8290, 3 ml T-1, Kimble Glass, Paramus, N.J.
[4] No. 541, Teflon-lined natural rubber stopper, 13 mm, West Rubber Co., Phoenixville, Pa.
[5] Multi-Temp block heater, No. 2093, Lab-Line Instruments, Melrose Park, Ill.
[6] Aminco-Bowman, American Instruments Co., Silver Spring, Md.

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Table I—Plasma Propiram Concentrations (Nanograms per Milliliter) after a Single Oral Administration of Propiram Fumarate Tablet or Solution (50-mg Base Equivalent) in Normal Subjects[a]

Dosage Form	Hours after Drug Administration											
	0.5	0.75	1	1.5	2	2.5	3	4	6	8	12	16	24
Solution	223.20 ±46.06 (65.26)[b]	276.00 ±51.72 (56.21)	287.20 ±36.02 (39.66)	285.70 ±29.49 (32.64)	237.30 ±24.50 (32.65)	236.56 ±32.35 (41.02)	208.00 ±21.46 (32.63)	179.88 ±21.27 (33.44)	171.67 ±23.53 (41.12)	84.56 ±10.91 (38.69)	52.80 ±13.39 (80.19)	29.20 ±9.75 (105.65)	17.20 ±7.40 (136.05)
Tablet	94.90 ±26.92 (89.70)[b]	187.11 ±29.99 (48.09)	257.70 ±24.13 (29.61)	300.70 ±27.88 (29.32)	219.70 ±22.13 (31.85)	189.70 ±19.02 (31.71)	197.60 ±20.31 (32.50)	173.40 ±16.13 (29.41)	145.20 ±16.44 (35.81)	114.30 ±15.93 (44.08)	61.10 ±12.81 (66.32)	31.70 ±8.47 (84.48)	21.80 ±8.04 (116.61)

[a] Data are reported as mean ± *SEM*, $n = 10$. [b] The numbers in parentheses are the coefficients of variation in percent of the mean.

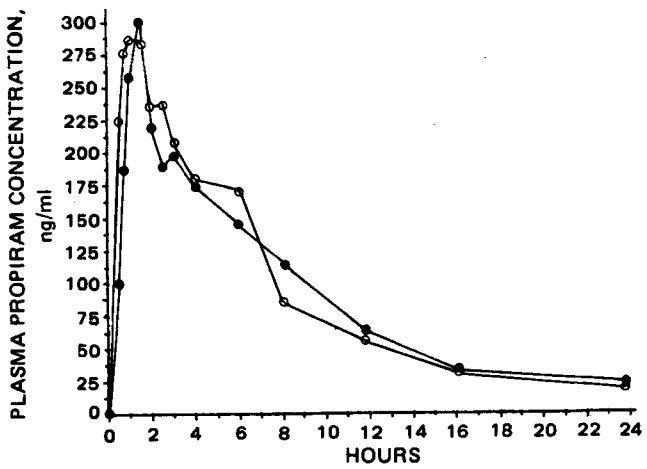

Figure 1—*Mean plasma propiram concentrations–time curve after a single oral administration of propiram fumarate (50-mg base equivalent) in normal subjects. Key: ●, tablet; and ⊖, solution.*

The drug concentration was determined from measured fluorescence in each sample by comparison with a calibration curve obtained with pure despropionylpropiram. The correction factor for differences in molecular weight between propiram and despropionylpropiram was applied.

Under the assay conditions, the detection limit for propiram, defined as the lowest point on the calibration curve producing a mean ± *SD* where the coefficient of variation did not exceed 10%, was 25 ng/ml. Levels below 25 ng/ml were estimated from the calibration curve.

Data Analysis—The plasma propiram concentration–time data from individual subjects were analyzed by CSTRIP (5) to obtain initial polyexponential parameter estimates. The computer stripping revealed that the individual data were described adequately by a biexponential equation. The coefficients and rate constants obtained then were used as preliminary estimates for further computer analysis by the nonlinear least-squares program NONLIN (6). Specific first-order rate constants for absorption (K_a) and elimination (K), as well as apparent volume of distribution (V_d), were obtained using the one-compartment open model with first-order absorption. The plasma concentration of drug (C_p) at any time (t) after a single dose (D) is described by:

$$C_p = \frac{FD}{V_d}\left(\frac{K_a}{K_a - K}\right)\left[e^{-K(t-t_{lag})} - e^{-K_a(t-t_{lag})}\right] \qquad \text{(Eq. 1)}$$

where F is the fraction of dose absorbed and t_{lag} is the absorption lag time (the time elapsed between dosing and the time of appearance of measurable plasma drug concentration).

The area under the plasma drug concentration–time curve from 0 to 24 hr ($AUC_{24\ hr}$) was calculated by the trapezoidal rule, and the total area (AUC_∞) was estimated by $AUC_{24\ hr} + C_{p,24\ hr}/K$, where $C_{p,24\ hr}$ is the estimated plasma drug concentration at 24 hr after drug administration. The observed maximum plasma drug concentration (C_{max}) and the time (T_{max}) to reach C_{max} were obtained from the individual plasma drug concentration–time data.

The total body clearance (Cl_{TB}) was calculated from the ratio of the administered dose to AUC_∞. The renal clearance (Cl_R) was calculated from the ratio of the cumulative urinary excretion (0–48 hr), $\Sigma Du_{48\ hr}$ to AUC_∞.

The estimated pharmacokinetic parameters of propiram for the two formulations were compared statistically *via* analyses of variance for crossover design.

RESULTS AND DISCUSSION

The mean plasma propiram concentrations with time for the tablet and solution are given in Table I and Fig. 1. A substantial intersubject variation in the plasma propiram concentration was observed at 30 min and 12 hr for both dosage forms (in which the coefficient of variation was >50% of the mean value). Similar variation in plasma concentration at 30 min was observed by Pütter and Kroneberg (3). The large variation in propiram concentration seen at the 24-hr sampling time in the present study may have been due to levels being near detection limits of the assay.

The individual plasma drug concentration–time data were fitted best by a one-compartment open model with first-order absorption. The mean

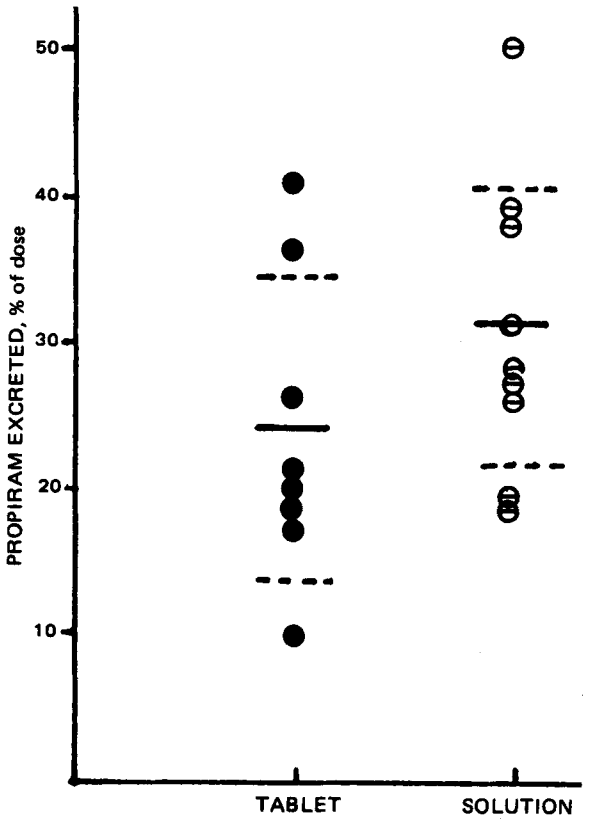

Figure 2—*Cumulative urinary excretion of propiram (0–48 hr) after a single oral administration of propiram fumarate (50-mg base equivalent) in normal subjects. Key:* ●, *tablet,* n = 8, *mean* ± SD = 24.3 ± 10.3; *and* ⊖, *solution,* n = 9, *mean* ± SD = 31.5 ± 10.0.

and standard errors of the estimated pharmacokinetic parameters of propiram for both dosage forms are presented in Table II. The data in Table II indicate that the drug was absorbed rapidly after administering either the tablet or solution with an apparent absorption rate constant (K_a) of 3.7 hr^{-1}; however, the t_{lag} of the tablet (0.34 hr) was longer than that of the solution (0.14 hr). The differences (0.2 hr) in the t_{lag} represent the disintegration–dissolution time of the tablet dosage form. Comparison of other pharmacokinetic–bioavailability parameters of the two dosage forms revealed no statistically significant differences ($p > 0.05$). This finding indicates that the dissolution rate of the propiram fumarate tablet is fast and may not be rate limiting in absorption. After oral administration, propiram was >97% absorbed (3). Thus, the fraction of dose absorbed (F) can be considered as unity.

The time to reach maximum plasma concentration (T_{max}) was 1.4 hr for the tablet and 1.2 hr for the solution. These values were in accord with literature data for the tablet (3). The maximum plasma drug concentrations (C_{max}) of propiram were similar with the two dosage forms: 308.3 ng/ml for the tablet and 342.3 ng/ml for the solution. The areas under the plasma drug concentration–time curves from 0 to 24 hr ($AUC_{24\ hr}$) were 2098.35 and 2150.73 (ng hr)/ml for the tablet and solution, respectively. The size of the area integral under the plasma levels *versus* time curve indicates that the same magnitude of bioavailability was obtained after either the tablet or solution dosage form.

Table II—Pharmacokinetic Parameters of Propiram after a Single Oral Administration of Propiram Fumarate Tablet or Solution (50-mg Base Equivalent) in Normal Subjects

Parameter	Tablet[a]	Solution[a]
C_{max}, ng/ml	308.30 ± 26.51	342.30 ± 29.33
T_{max}, hr	1.38 ± 0.09	1.20 ± 0.19
$AUC_{24\ hr}$, ng·hr/ml	2098.35 ± 269.65	2150.73 ± 300.25
AUC_{∞}, ng·hr/ml	2219.52 ± 323.75	2234.70 ± 342.46
Cl_{TB}, ml/min	444.30 ± 58.02	441.31 ± 53.55
$\Sigma Du_{48\ hr}$, % of dose	24.34 ± 3.65	31.59[c] ± 3.34
Cl_R, ml/min	105.17[b] ± 22.53	124.77[c] ± 14.23
K_a, hr^{-1}	3.68 ± 0.48	3.67 ± 0.62
K, hr^{-1}	0.15 ± 0.02	0.18 ± 0.02
$t_{1/2K_a}$, hr	0.22 ± 0.03	0.27 ± 0.05
$t_{1/2K}$, hr	5.17 ± 0.58	4.35 ± 0.47
V_d, liters/kg	2.31 ± 0.16	1.94 ± 0.09
t_{lag}, hr	0.34[d] ± 0.05	0.14 ± 0.06

[a] Mean ± *SEM* of 10 subjects. [b] Mean of eight subjects. [c] Mean of nine subjects. [d] Statistically significant ($p < 0.05$) when the tablet was compared to the solution *via* analysis of variance.

A large distribution volume (2.3 liters/kg for the tablet and 1.9 liters/kg for the solution) indicates extensive metabolism and/or distribution. The disposition (elimination) half-life (5.17 hr for the tablet and 4.35 hr for the solution) obtained was lower than the value (~7 hr) reported by Horster *et al.* (4) using a ^{14}C-labeled propiram fumarate tablet.

The cumulative amounts of propiram excreted in the 0–48-hr urine ($\Sigma Du_{48\ hr}$) after the tablet and solution are compared in Fig. 2. The mean $\Sigma Du_{48\ hr}$ after the tablet (24.34%) was not significantly different ($p > 0.05$) from that after the solution (31.59%), showing that approximately one-third of the administered dose was recovered in the urine as unchanged propiram. A substantial intrasubject variation in $\Sigma Du_{48\ hr}$ values, as seen in Fig. 2, may have been due to the degree of metabolism differences among the subjects.

For both the tablet and the solution, total body clearance (444 and 441 ml/min) was much greater than renal clearance (105 and 125 ml/min), indicating that metabolic clearance is a major route of the drug disposition in humans.

REFERENCES

(1) V. F. Hoffmeister, G. Kroneberg, U. Schlichting, and W. Wuttke, *Arzneim.-Forsch.*, **24**, 600 (1974).

(2) V. B. Duhm, W. Maul, H. Medenwald, K. Patzschke, and L. A. Wegner, *ibid.*, **24**, 632 (1974).

(3) V. J. Pütter and G. Kroneberg, *ibid.*, **24**, 643 (1974).

(4) V. F. A. Horster, B. Duhm, W. Maul, H. Medenwald, K. Patzschke, and L. A. Wegner, *ibid.*, **24**, 652 (1974).

(5) A. J. Sedman and J. G. Wagner, *J. Pharm. Sci.*, **65**, 1006 (1976).

(6) C. M. Metzler, G. L. Elfring, and A. J. McEwen, "NONLIN 2 and Associated Programs," Upjohn Co., Kalamazoo, Mich., 1975.

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